Low-grade follicular lymphoma involvement of the bone marrow with a mixed paratrabecular, diffuse, and massive pattern expressing typical mantle cell lymphoma immunophenotype CD23-/FMC7+: a case report

TO THE EDITOR: Follicular lymphoma (FL) is the second most common lymphoma diagnosed in the USA and Western Europe, accounting for approximately 35% of all non-Hodgkin lymphomas [1], but only 2.9% of non-Hodgkin lymphomas in Korea [2]. As previously reported, typical bone marrow (BM) involvement in FL is characterized by paratrabecular infiltration, which is reportedly found in 86.1% of all cases [3, 4]. The frequency of BM involvement is reportedly higher in grade 2 or 3 (33.0 and 28.5%) FL than in low-grade (grade 1, 17.0%) FL [4]. By contrast, diffuse and massive BM involvement was reportedly correlated with more aggressive disease type including diffuse large B cell lymphoma and Burkitt/Burkitt-like lymphoma [4]. Since CD23-/FMC7+ is the typical immunophenotype presentation in mantle cell lymphoma (MCL), we report a case of BM involvement with low-grade FL and a mixed paratrabecular, diffuse, and massive pattern expressing typical MCL immunophenotype CD23-/FMC7+, in addition to a review of the literature [4-7]. To our knowledge, this is the first report of low-grade FL with mixed BM involvement including paratrabecular, diffuse, and massive pattern expressing typical MCL immunophenotype CD23-/FMC7+ in Korea.

A 48-year-old woman was admitted with both leg edema and multiple lymphadenopathy. Complete blood count on admission showed leukocytosis (white blood cells, 30.95×10^9/L; hemoglobin, 12.5 g/dL; and platelet count, 186.0×10^9/L) and peripheral blood smear showed predominance of small-to-medium neoplastic lymphoid cells with cleaved nuclei and scant amount of cytoplasm (87%) (Fig. 1A). BM examination for a lymphoma staging work up was performed, and aspirate and touch print showed hypercellular marrow with increased infiltration of neoplastic lymphoid cells (53.0%) with similar morphologic features (Fig. 1B, C). Flow cytometry was performed and neoplastic lymphoid cells showed only one population expressing intermediate positivity for HLA-DR (71.7%), CD10 (66.0%), CD19 (68.9%), CD20 (87.4%), CD22 (63.9%), FMC7 (48.5%), kappa light chain (89.5%), and lambda light chain (42.9%), with kappa light chain predominance beyond lambda light chain in terms of strength of positivity. Positivity was not shown for CD5 or CD23. BM biopsy showed hypercellular marrow with diffuse infiltration by neoplastic lymphoid cells. Paratrabecular infiltration by neoplastic lymphoid cells was identified in the majority of BM involved paratrabecular areas, but diffuse and massive infiltration by neoplastic lymphoid cells was also identified in the intertrabecular areas (Fig. 1D). Subsequently immunohistochemistry (IHC) staining showed strong membranous positivity for CD20 and nuclear positivity for BCL6 in the neoplastic lymphoid cells found in paratrabecular areas, but neoplastic lymphoid cells found in intertrabecular areas also showed weak nuclear positivity for BCL6, accompanied by strong membranous positivity for CD20. CD3, CD5, and cyclin D1 were negative in all neoplastic lymphoid cells (Fig. 1E–I). Karyotype analysis was normal and subsequent fluorescence in situ hybridization for the detection of *CCND1* rearrangement showed negative results. The patient had lymphadenopathy involving bilateral parotid, cervical, axillary, internal mammary, mediastinal, hilar/interlobar, peritoneal, retroperitoneal, common/internal/external iliac, and inguinal regions, as well as hepatosplenomegaly at diagnosis. Pathologic diagnosis performed with left inguinal lymph node excisional biopsy showed positivity for BCL2 (in cytoplasm), BCL6 (in the nucleus), CD10 (on membranes), CD20 (on membranes), and Ki-67 (20% in the nucleus), but negative results for CD3, CD5, and cyclin D1 IHC staining. Thus, a pathologic diagnosis of low-grade FL (grade 1) was made, with clinical stage 4SHMEB. The patient received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for chemotherapy, and was discharged to routine follow-up.

FMC7 is an antigen detected on certain subgroups of neoplastic and normal B cells that originate from later stages of B cell maturation, and CD23 is a low-affinity IgE receptor belonging to the superfamily of type II membrane protein expressing the lectin-binding motif [5]. A study that analyzed the diagnostic usefulness of CD23 and FMC7 expression in B-lineage lymphoma [5] reported that 98.4% of FL patients showed either FMC7+ or FMC7± immunophenotype, and the frequency of CD23+/FMC7+, CD23-/FMC7+ and CD23-/FMC7- immunophenotype in FL was 72.6%, 25.8%, and 1.6%, respectively. By contrast, this study reported that the frequency of CD23-/FMC7+ immunophenotype in MCL was 100% [5]. This indicates that although CD23-/FMC7+ is a typical MCL immunophenotype, the same results can be found in FL with the reported frequency of 25.8%, as in our case; therefore, the presence of CD23-/FMC7+ immunophenotype cannot be used as a confirmatory result for the diagnosis of MCL.

Although the typical pattern of BM involvement in FL was reportedly paratrabecular, and was identified in 86.1% of FL and 90.1% of all FL samples with only paratrabecular BM involvement [6], a mixed pattern that was defined as the presence of 2 patterns, e.g., a paratrabecular and another pattern (diffuse, nodular, or interstitial), was also reportedly present in FL cases [6]. Another study also reported that the frequency of BM involvement in FL was purely paratrabecular (43.3%), mixed (42.8%), or purely non-paratrabecular (13.9%) [7]. Since BM involvement in FL is more

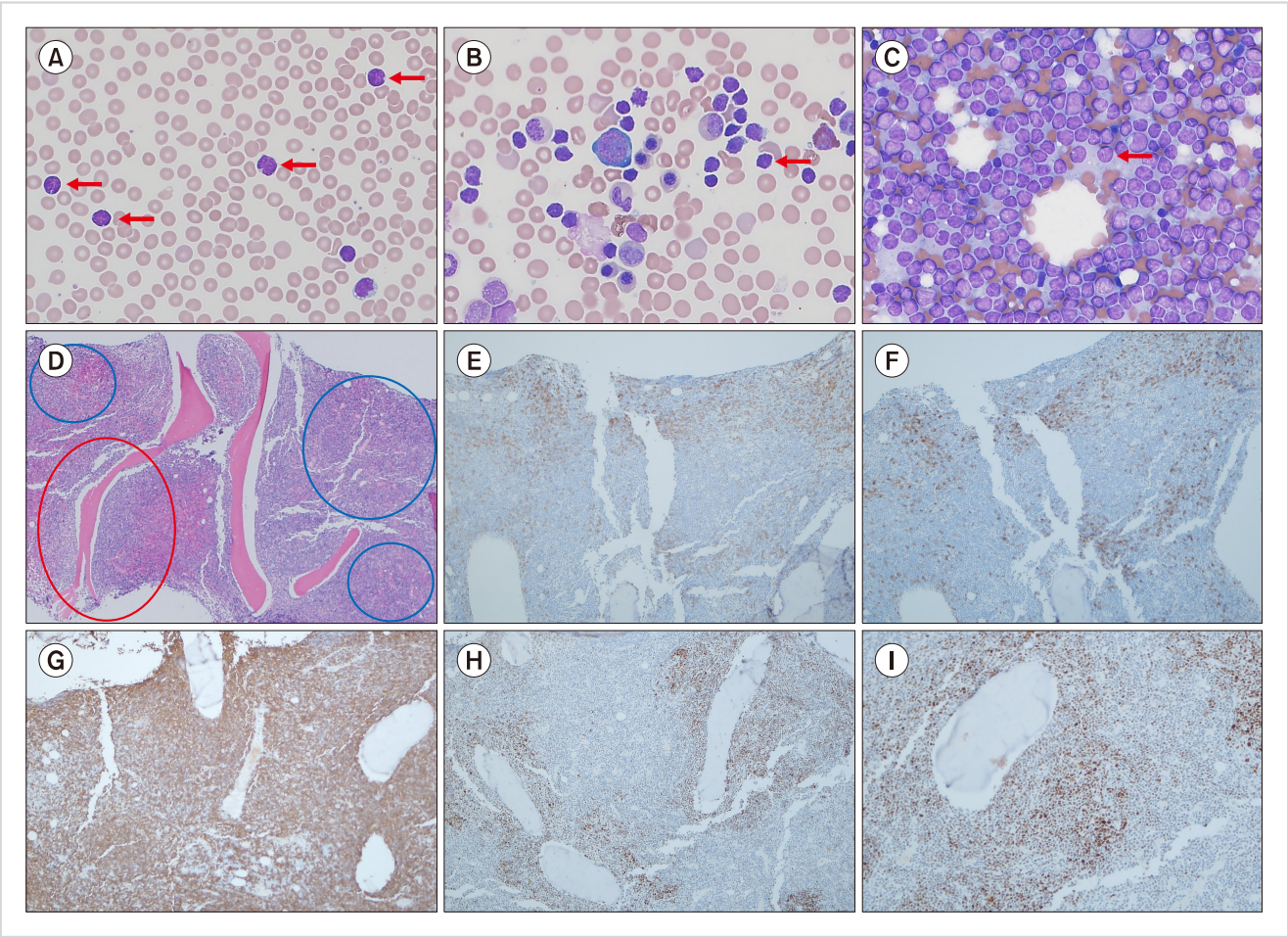

Fig. 1. Peripheral blood smears, bone marrow aspiration and touch print, bone marrow biopsy, and immunohistochemical staining results of our case. **(A)** Neoplastic lymphoid cells found in peripheral blood smear showed small-to-medium, cleaved nuclei and scant amount of cytoplasm (indicated by red arrows, Wright-Giemsa stain, ×400). **(B)** Neoplastic lymphoid cells found in the bone marrow aspirates also showed a small-to-medium, cleavage nucleus, and scant amount of cytoplasm as morphologic features (indicated by red arrows, Wright-Giemsa stain, ×400). **(C)** Neoplastic lymphoid cells found in touch print of the bone marrow also showed similar morphologic features (indicated by red arrows, Wright-Giemsa stain, ×400). **(D)** Bone marrow biopsy section showed infiltration of neoplastic lymphoid cells with a mixture of paratrabecular (indicated by red circle) and intertrabecular (indicated by blue circles) infiltration pattern (hematoxylin and eosin stain, × 100). **(E, F)** Neoplastic lymphoid cell did not show positivity on CD3 and CD5 immunohistochemical staining (×100). **(G)** However, neoplastic lymphoid cells showed strong membranous positivity for CD20 immunohistochemical staining (×100). **(H, I)** Neoplastic lymphoid cells found in paratrabecular areas showed strong nuclear positivity for BCL6, but those found in intertrabecular areas showed weak nuclear positivity for BCL6 (×100 and ×200, respectively).

frequently found in high-grade FL than in low-grade FL, our case has unique features, because the patient was diagnosed with low-grade FL but showed mixed BM involvement with a paratrabecular, diffuse, and massive pattern, with flow cytometry showing the presence of typical MCL immunophenotype CD23-/FMC7+. Therefore, it would be important to know that BM involvement in FL can be mixed, consisting of a paratrabecular and another pattern, e.g., diffuse and massive, as well as typical paratrabecular only.

Composite lymphoma is defined as the simultaneous presence of 2 morphologically and immunophenotypically different lymphomas at the same site, and a case with composite FL and MCL has been reported [6]. The coexistence of MCL and FL has been reported in 12 cases; most showed 2 lymphomas adjacent to each other and 1 showed an intermixed pattern of CD5-negative MCL and FL [8]. Although our case showed typical MCL immunophenotype CD23-/FMC7+, *CCND1* rearrangements, which are diagnostic findings in MCL, were not present. These results suggest that our case did not have sufficient diagnostic evidence of MCL; therefore, it can be concluded that the diagnosis of composite MCL and FL was not appropriate in our case.

In conclusion, we report a case of BM involvement by low-grade FL with a mixed paratrabecular, diffuse, and massive pattern expressing typical MCL immunophenotype CD23-/FMC7+. To our knowledge, this is the first such case report in Korea.

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No potential conflicts of interest relevant to this article were reported.

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